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Macrocytic Anemia and Thrombocytosis Associated With Thymoma: A Case Report

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Thymomas are often associated with autoimmune disorders. We report on a 45-year-old female patient with thymoma and hypogammaglobulinemia (Good's syndrome) who developed symptomatic macrocytic anemia (Hb 4.4 g/dl, MCV 112 fl) and thrombocytosis (Plt 442 G/l). Besides hypogammaglobulinemia (IgG 589 mg/dl), an inverted ratio of $CD4^+$/$CD8^+$ cells was seen. The bone marrow biopsy showed a slightly hypercellular bone marrow with normal granulopoiesis, normal megakaryopoiesis and a mild dyserythropoiesis without any ring-sideroblasts. The in-vitro stem cell culture from the bone marrow revealed an atypical growth of macroclusters, reduced BFU-E and CFU-GEMM colony growth, whereas the CFU-GM colony growth was within the normal range. The chromosomal analysis showed a normal karyotype. The plasma vitamin B_{12} and folate levels were within normal ranges, and we could not detect any autoantibodies. These findings excluded the differential diagnoses pure red cell aplasia (PRCA) and pernicious anemia. After resection of the thymoma of mixed cell type, the macrocytic anemia and thrombocytosis disappeared. The clinical course was complicated by a cerebral palsy and a life-threatening fungal septicemia after surgery. In the third year after thymectomy, hyporegenerative macrocytic anemia and thrombocytosis reappeared and an immunosuppressive treatment with prednisolone (1 mg/kg BW) was started. After initiation of the prednisolone therapy, reticulocyte counts increased and macrocytic anemia as well as thrombocytosis disappeared. The normalization of these laboratory parameters during glucocorticoid therapy suggests that in rare cases the constellation of macrocytic anemia, thrombocytosis and hypogammaglobulinemia may be due to an underlying immunologic mechanism. Am. J. Hematol. 63:38–41, 2000. © 2000 Wiley-Liss, Inc.

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INTRODUCTION

Thymomas are often associated with autoimmune diseases including myasthenia gravis, poly-myositis, hypogammaglobulinemia, and various cytopenias [1–6]. These cytopenias include agranulocytosis, pure red cell aplasia (PRCA), and aplastic anemia [7–12]. PRCA is characterized by normochromic, normocytic anemia, reticulocytopenia, and the absence of erythroblasts from an otherwise normal bone marrow [13]. In contrast to PRCA which is characterized by a very selective anemia, aplastic anemia results in pancytopenia due to global marrow aplasia [14,15]. Often, the immunoassociated symptoms like PRCA disappear after thymectomy but reappear after a latency period even without recurrence of thymoma [6,16]. We report an unusual case of macrocytic anemia, thrombocytosis and hypogammaglobulinemia in the presence of thymoma, which could not be classified as

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any of the blood diseases which have been described in association with thymoma so far.

CASE REPORT

In June 1994, a 45-year-old female presented with symptoms of anemia expressed by pallor, dyspnoe, fatigue, retrosternal pain, and palpitation during exercise, which had increased constantly during the last two months. The physical examination was unremarkable with no lymphadenopathy or splenomegaly. The laboratory study revealed: hemoglobin (Hb) 4.4 g/dl, red blood cells (RBC) 1.17 T/l, MCV 112 fl, reticulocytes 1.17 G/l, leucocytes 6.4 G/l, and platelets (Plt) 442 G/l. In addition, hypogammaglobulinemia (IgG 589 mg/dl) was diagnosed. The CT scan revealed a retrosternal mass in the left paramedian mediastinum, and in July 1994 the patient underwent surgery. An encapsulated mediastinal tumor with an extension to the left mediastinal pleura, which caused atelectasis of the left upper lobe, was entirely resected. The histological examination showed a thymoma of mixed cell type with cortical and medullary components. The extension of the tumor met the criteria of stage I [8]. The surgery was complicated by a cerebral palsy with signs of ischemia in supra- and infratentorial as well as in thalamic regions. This resulted in left-sided cerebellar symptoms with ataxia of the extremities, nausea, low convergence response of the bulbi and aphasia. These neurological symptoms improved during the first week after surgery. Ten days after surgery the patient developed septic fever. The serological findings revealed a high titer of candida albicans antibodies (1:>5000), and streptococcus and staphylococcus epidermidis were detected in the blood culture. Besides, a persistent hypogammaglobulinemia, a decreased number of B-cells (0.02 G/l) and an inverted ratio of $CD4^+/CD8^+$ cells ($CD4^+$, 0.77 G/l; $CD8^+$, 0.99 G/l) were seen. Despite treatment with antibiotics (penicillin G, combactam, vancomycin, and netilmycin) and antimycotics (amphotericin B) and despite immunoglobulin substitution, the fever did not disappear for 3 months. Besides further improvement of neurological symptoms, the blood counts returned to normal values and the hypogammaglobulinemia had improved by December 1994. One year later, in December 1995, the patient was able to return to work. In summer 1996, the control investigation showed the following laboratory parameters: IgG 725 mg/dl, Hb 13.6 g/dl, RBC 3.87 T/l, MCV 103.6 fl, Plt 502 G/l. In January 1997, the patient again suffered from dyspnea, fatigue, pulse synchronic tinnitus, and palpitation during exercise. The laboratory findings confirmed the recurrence of macrocytic anemia, reticulopenia (RBC 2.59 T/l, Hb 9.9 g/dl, MCV 113.5 fl, reticulocytes 12.95 G/l), and thrombocytosis (Plt 572 G/l). Treatment with vitamin B_{12} and iron substitution was initiated without success. The bone marrow histology and aspiration in March 1997 showed a slightly hypercellular bone marrow with normal granulocytopoiesis, normal megakaryocyte density, and mild dyserythropoiesis. The in vitro stem cell culture from the bone marrow showed an atypical growth of macroclusters, reduced growth of burst-forming units-erythroid (BFU-E; 100 colonies/10^5 MNC, normal range: 128–474 colonies/10^5 MNC) and granulocyte-erythrocyte-macrophage-megakaryocyte CFUs (CFU-GEMM; 0 colonies, normal range: 2–22 colonies/10^5 MNC) whereas the growth of granulocyte-macrophage colony-forming units (CFU-GM) was within the normal range (145 colonies/10^5 MNC, normal range: 102–574 colonies/10^5 MNC). No chromosomal abnormalities were detected, and a clonal B or T cell population was excluded by polymerase chain reaction. The serological findings of double-stranded DNA, antinuclear antibodies, anticardiolipin antibodies of IgG, and IgM type were within the normal range, as was the activity of anticoagulant factors like protein C, protein S, and antithrombin III. No factor V Leiden mutation or lupus anticoagulant could be detected. In addition, the following autoantibodies were negative or within the normal range: peripheral and cytoplasmic antineutrophil cytoplasmic antibodies (c-ANCA and p-ANCA), antibodies against parietal cells, antibodies against smooth muscles, antimitochondrial antibodies, antithyroglobulin antibodies, and antithyroid microsomal antibodies. Due to the negative coombs test and the normal haptoglobin, normal indirect bilirubin and normal LDH level, hemolysis was excluded. The low reticulocyte counts indicated an impaired regeneration of RBC. The MRT scan showed no signs of recurrence of the thymoma. In August 1997, immunosuppressive treatment with prednisolone (1 mg/kg BW) was started. After initiation of prednisolone therapy, the reticulocyte counts, and hemoglobin levels normalized and the macrocytosis and thrombocytosis disappeared (Fig. 1). After 3 months, prednisolone therapy was withdrawn. By that time, the stem cell growth of the peripheral blood had also normalized (CFU-GM, 339 colonies/ml, normal range, 50–936 colonies/ml; BFU-E, 1426 colonies/ml, normal range, 120–1862 colonies/ml; CFU-GEMM, 71 colonies/ml, normal range, 4–77 colonies/ml), whilst gammaglobulin levels (IgG: 536 mg/dl) still remained at a low level.

DISCUSSION

The present case report suggests that macrocytic anemia and thrombocytosis may occur as symptoms of autoimmunity in association with thymoma. An autoimmune pathomechanism seems to be likely, since the macrocytosis and thrombocytosis normalized after the patient had recovered from the thymectomy and these paremeters also disappeared shortly after the application of pred-

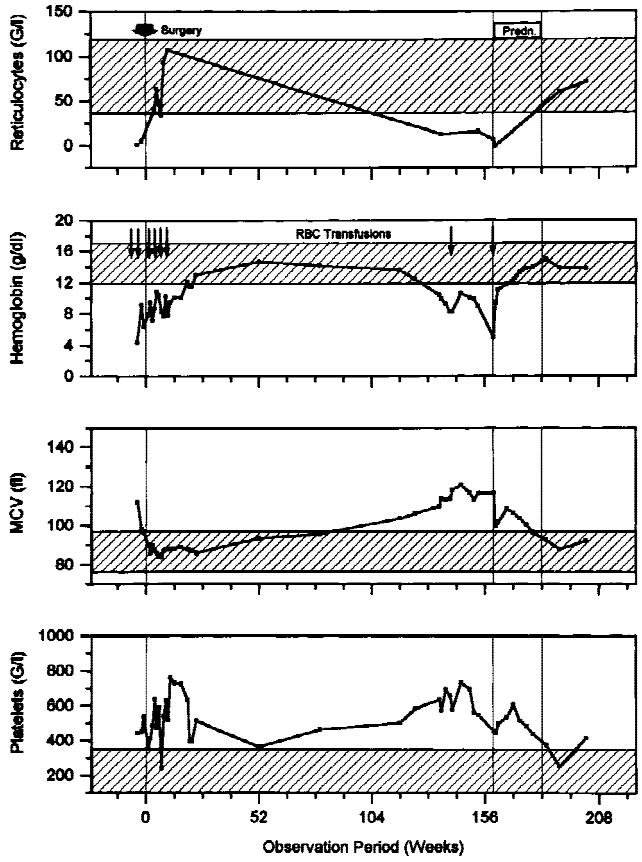

Fig. 1. Evolution of reticulocyte counts, hemoglobin levels, median corpuscular volume (MCV) and platelet counts in a patient after resection of thymoma (surgery) and prednisolone therapy (Predn.).

nisolone. Thymoma was accompanied in our patient by hypogammaglobulinemia, a phenomenon which occurs in about 10% of thymoma patients and has been termed as Good's syndrome [17]. The clinical course in our patient indicates a previously undocumented constellation of macrocytic anemia and thrombocytosis associated with thymoma since the bone marrow morphology did not fulfill the diagnostic criteria of PRCA and since the differential diagnosis of pernicious anemia could be excluded. Only one previously reported case showed thrombocytosis due to PRCA associated with thymoma which was confirmed by the characteristic aplasia of RBC precursors in the bone marrow [7]. In our case an elevated platelet count was present when thymoma was diagnosed, and at that time secondary thrombocytosis could be excluded by exclusion of iron deficiency, chronic inflammation, myeloproliferative disorders or myelodysplastic syndrome. In addition to the humoral immunodeficiency, our patient had an inverted ratio of $CD4^+/CD8^+$ lymphocytes. Similar to previously reported cases, the immunodeficiency in our patient might have been responsible for the life-threatening fungal septicemia after surgery [18]. Although anticardiolipin antibodies sometimes reflect immune dysregulation under the influence of thymic alteration, an elevated titer of anticardiolipin antibodies was not responsible for the ischemic stroke during surgery in our patient, rather the thrombocytosis might have contributed to the predisposition for thrombosis [19].

The response to immunosuppressive treatment with prednisolone in the present case is in line with response rates of PRCA in previously reported cases, which have shown only a slightly impaired in-vitro stem cell growth [16]. Another favorable prognostic parameter in our patient seems to be the absence of a clonal T-cell population, since the presence of a clonal T-cell population has been shown to be associated with an unfavorable prognosis in some cases of PRCA associated with thymoma [20]. However, in some cases clonal T-cell populations have been detected only intrathymically, an investigation which was not done in the present case. Therefore, the presence of a clonal T-cell population cannot be definitely excluded in our patient [21]. Although the present case was not investigated for autoreactive T-cells and autoantibodies could not be detected, the recurrence of macrocytosis and thrombocytosis without thymoma recurrence implies, as suspected previously, that there is an extrathymic site of autoantibody production [22]. In conclusion, this case report shows that glucocorticoid treatment may be beneficial in rare cases with macrocytic anemia and that autoimmunity may be considered as the initiating pathomechanism of macrocytosis and thrombocytosis in association with thymoma.

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